UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/621,269	07/15/2003	Philip E. Thorpe	4001-003000/UTSD:0893 US	4853

52101 7590 10/09/2007

PEREGRINE PHARMACEUTICALS, INC.
5353 WEST ALABAMA
SUITE 306
HOUSTON, TX 77056

EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
10/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/621,269	THORPE ET AL.	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,23,51,52,94,96-99,102,105-107,111,112,115-117 and 120-122* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *106,112,117 and 122* is/are allowed.

6)☒ Claim(s) *1-19,23,51,52,94,96-99,102,105,107,111,115,116,120 and 121* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/10/07, 3/23/07, 6/12/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed July 16, 2007 in response to the Office Action of January 12, 2007, is acknowledged and has been entered. Previously pending claims 1, 9-12, 23, 94, 96, 97-99, 102, 107, 115, 120, and 122 have been amended. Claims 1-19, 23, 51, 52, 94, 96-99, 102, 105-107, 111, 112, 115-117, and 120-122 are currently pending and being examined.

New Rejections

(based on new considerations)

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-19, 23, 51, 52, 94, 96-99, 102, 105, 107, 111, 115, 116, 120, and 121 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to

practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to composition comprising a purified antibody, or antigen-binding fragment thereof, wherein said antibody **binds to phosphatidylserine (PS)** and has substantially the same phospholipid binding profile as the monoclonal antibody 3G4, as determined by relative strength of reactivity in an ELISA, is PS=PA=PI=PG=CL>>PE, wherein > indicates at least 2-fold difference in phospholipid binding and >> indicates at least 10-fold difference in phospholipid binding, each at identical antibody concentrations; or an affinity for PS of at least equal to the affinity of 3G4 for PS; wherein the affinity of 3G4 for PS, as determined in said ELISA, has an EC_{50} value of 0.040 ug/ml; and wherein said ELISA comprises (i)-(iv) of claim 1 (claims 1-19, 23, 51, 52, 102, 105), wherein said antibody further **binds to PA, PI, PG, CL or PE** and effectively competes with 3G4 for binding to these phospholipids (claims 2-8),

wherein said antibody is an **Fab' or Fab** antibody (claim 15), wherein said antibody is the monoclonal antibody 3G4 (claim 105); a composition comprising a purified antibody that **binds to PS** and has substantially the same phospholipid binding profile as 3G4 (claim 94); a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a biologically effective amount of a purified antibody or antigen-binding fragment thereof, wherein said antibody is an antibody **as defined in claim 1** (claim 96), the pharmaceutical composition of claim 96 wherein said antibody is 3G4 (claim 111); a purified antibody, or antigen-binding fragment thereof, wherein said antibody **binds to PS**, and has substantially the same phospholipid binding profile as 3G4 (claim 97, 115), the purified antibody of claim 97 wherein said antibody is 3G4 (claim 116); a hybridoma that produces a monoclonal antibody that **binds to PS** and has substantially the same phospholipid binding profile as 3G4 (claim 98, 120), the hyrbidoma of claim 98 wherein said antibody is 3G4 (claim 121); a method for preparing an antibody **as defined in claim 97** comprising immunizing an animal with activated endothelial cells and selecting from the immunized animal an antibody **as defined in claim 97** (claim 99); a composition comprising a purified antibody, wherein a human antibody framework or constant region is operatively attached to an antigen-binding region of an antibody that **binds to PS** and effectively competes with the monoclonal antibody 3G4 for binding to PS in an ELISA that comprises (a)-(d) of claim 107 (claim 107).

The specification discloses anti-tumor effects of antibodies 3SB, 9D2, and 3G4 for mice bearing tumors (Figs 6-8). The specification discloses that antibody 3G4 or human chimeric 3G4 (ch3G4) can enhance the survival of mice infected with murine

CMV (Fig. 27; p. 308, lines 1-7; Example XXI, p. 315). Figures 18A and 18B disclose the SEQ ID NOs for antibody 3G4 variable heavy and light chains as well as the CDRs encompassed by the chains (see specification amendment to p. 54-55 and p. 309, mailed 7/16/2007). Table 4 lists anti-PS antibodies and their specificity to different anionic phospholipids and aminophospholipids, wherein the specificity of 3G4 for phospholipids is PS=PA=PI=PG=CL>>PE (p. 246). Table 2 lists the serum-dependence of anti-PS antibodies (p. 243). After filing of the instant application, Applicants later discovered they were incorrect with regards to the serum dependence of at least 2 antibodies listed in Table 2. An amendment to Table 2 was entered 10/18/2006 that changed the serum dependence of antibodies 3G4 and 3B10 from serum-independent to serum-dependent, meaning these antibodies require the presence of serum in order to bind to aminophospholipids. The second declaration by Philip Thorpe under 37 CFR 1.132, dated 7/16/2007 teaches that 3B10 is now known to be serum-dependent and Exhibit B demonstrates that FBS was required for antibody binding.

Table 2 currently lists only two antibodies as serum-*independent* for binding to PS: antibodies 3SB and 9D2. The specification discloses that antibody 3SB was produced as described by Rote et al (Clinical Immunology and Immunopathology, 1993, 66:193-200, IDS) (p. 242, lines 5-10). The specification discloses that 3SB recognizes PS on intact cells in the presence and absence of serum (p. 246, lines 17-22), however no data is provided, at least in the specification, to show that either 3SB or 9D2 can bind aminophospholipids in the *absence* of serum.

The art teaches that antibodies previously thought to bind aminophospholipids actually bind lipid-bound serum or plasma proteins. Bevers et al (Clinical Immunology, 2004, 112:150-160) teach that the most frequently occurring antigens are the lipid-bound plasma proteins β_2-glycoprotein I (β_2GPI) and prothrombin (PT), although several other lipid-bound plasma proteins have been reported as antigens for antiphospholipid antibodies (abstract). Both proteins bind to anionic phospholipids, mainly PS, which becomes exposed at the surface of activated platelets, apoptotic cells, or cell-derived microparticles (abstract). Bevers et al teach that the term 'antiphospholipid antibody' is a misnomer and the term 'anti-lipid-bound β_2GPI' antibody or 'anti-lipid-bound-PT' antibody would be more appropriate (p. 150, col. 2 last paragraph bridging to p. 151). Bevers et al teach that several studies demonstrate that binding of β_2GPI to a phospholipids surface is accompanied by a conformational change, which could result in the exposure of cryptic epitopes (p. 152, col. 2). Figures 1 and 3 of Bevers et al illustrate that antibodies actually bind to β_2GPI or PT, wherein antibodies frequently bind more than one lipid-bound β_2GPI or PT. High lateral mobility of a monovalent lipid-bound anti- β_2GPI- β_2GPI complex allows this complex to engage another lipid-bound β_2GPI molecule to form a trimolecular complex (p. 153, col. 1; Fig 1A). Anti-PT antibodies may even be directed to a combined lipid-protein epitope or to neo-epitopes that may arise from conformational changes in membrane-bound prothrombin (p. 155, col. 1-2). Bevers et al further teach that the affinity of β_2GPI is strongly dependent on the molecular percent of anionic phospholipids and that increasing the content of PS from 5 to 20 molecular percent causes the dissociation constant to decrease by two

orders of magnitude. Change of the polar headgroup moiety does not significantly alter the affinity, provided the net negative charge density remains the same. For example, the dissociation constant for membranes with 10 molecular percent cardiolipin, which has two negative charges, is comparable to that of a surface with 20 molecular percent phosphatidylserine, having one net negative charge (p. 151, col. 2; Table 1).

Luster et al (J Biological Chemistry, 2006, 281:29863-71, IDS) and Ran et al (Clinical Cancer Research, 2005, 11:1551-1562, IDS) teach that antibody 3G4, the same 3G4 antibody recited the instant claims, requires β_2GPI for binding to PS. Luster et al further teach that dimeric β_2GPI complexes have increased binding for PS, while monomeric β_2GPI binding to PS was negligible. Antibody 3G4 binds to β_2GPI and promotes the formation of β_2GPI dimmers, which in turn, have increased avidity for PS (p. 7, col. 1 and 2). Luster et al teach that 3G4 Fab' fragments do not bind endothelial cells with exposed PS, but 3G4 F(ab')$_2$ fragments could bind, indicating that monomeric 3G4 Fab'/ β_2GPI complexes do not bind endothelial cells with exposed PS and that 3G4/β_2GPI binding to PS is dependent on dimeric complexes of β_2GPI (abstract; p. 7, col. 2).

One cannot extrapolate the disclosure of the specification to the enablement of the claims with regards to antibodies that bind PS, PA, PI, PG, CL or PE phospholipids because the art (Bevers et al, Luster et al, and Ran et al, above) teaches "aminophospholipid antibodies" do not actually bind to aminophospholipids as currently claimed, but rather bind to serum proteins such as β_2GPI and PT. The specification recognizes that the binding of some antibodies to aminophospholipids is dependent on

the presence of serum such as FBS, however, the art teaches that these antibodies are not actually binding to the aminophospholipids, they are binding to serum proteins. Given the teaching of the art (Luster et al, and Ran et al, above), it is clear that 3G4 does not bind aminophospholipids, but rather, binds β_2GPI to form β_2GPI complexes that increase avidity for β_2GPI to PS. Therefore the antibodies demonstrated to function in treating a viral infections, angiogenesis, or tumors in the specification do not actually bind PS, PA, PI, PG, CL or PE as required by the claims.

Further, one cannot extrapolate the disclosure of the specification to the enablement of the claims with regards to antibodies that comprise a F(ab') fragment, particularly with regards to antibody 3G4. The art teaches that a F(ab') fragment of 3G4 did not promote β_2GPI binding to PS because divalent complexes of β_2GPI are required for PS binding. Hence, a F(ab') fragment of at least antibody 3G4 would not only fail to bind to PS for the reasons set forth above, it would fail to produce complexes of β_2GPI required for β_2GPI binding to PS, and ultimately fail to function as a pharmaceutical as claimed and contemplated.

With regards to an antibody that binds to PS, PA, PI, PG, CL or PE and has substantially the same phospholipid binding profile as 3G4, it is clear from the teaching in the art (see Luster et al, and Ran et al, above) that 3G4 does not actually bind to PS or other aminophospholipids, hence one of skill in the art would not know how to make and use an antibody that could bind PS and have substantially the same phospholipid binding profile as 3G4 that would function as claimed and contemplated. Further, the art (Bevers et al above) teach that the affinity of β_2GPI for phospholipids is strongly

dependent on the molecular percent of anionic phospholipid. As stated above, increasing the content of PS from 5 to 20 molecular percent causes the dissociation constant to decrease by two orders of magnitude. Change of the polar headgroup moiety does not significantly alter the affinity, provided the net negative charge density remains the same. For example, the dissociation constant for membranes with 10 molecular percent cardiolipin, which has two negative charges, is comparable to that of a surface with 20 molecular percent phosphatidylserine, having one net negative charge (p. 151, col. 2; Table 1). Given the significant effect the percent concentration and polar headgroups have on the affinity of serum proteins for the aminophospholipids, the concentrations of the phospholipids in the claimed ELISAs would significantly alter the binding affinities of the claimed antibodies for the phospholipids because these antibodies are actually binding to the serum proteins. The fold-difference in binding affinity in the ELISA as claimed would be dependent on the concentrations of phospholipids and their polar headgroups, of which the concentrations or relative concentrations of each phospholipid are unknown in the claimed ELISAs. Given the variability in affinity of the serum proteins for the phospholipids based on polar headgroups and varying phospholipid concentrations, one of skill in the art would be subject to undue experimentation to screen for antibodies with the phospholipid binding profiles as claimed. Screening assays do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays, are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

As stated above, Table 2 of the specification currently lists only two antibodies as serum-independent for binding to PS: antibodies 3SB and 9D2. The specification discloses that antibody 3SB was produced as described by Rote et al (Clinical Immunology and Immunopathology, 1993, 66:193-200, IDS) (p. 242, lines 5-10). The specification discloses that 3SB recognizes PS on intact cells in the presence and absence of serum (p. 246, lines 17-22), however no data is provided, at least in the specification, to show that either 3SB or 9D2 can bind aminophospholipids in the *absence* of serum. Rote et al teach that they produced antibodies, including 3SB by immunizing mice with phospholipids micelles prepared from PS (p. 193, col. 2; p. 194, col. 1) and use FBS in the ELISAs for detecting binding of 3SB to PS (p. 194, col. 1). Rote et al produced antibodies in the presence of serum proteins and tested their binding in ELISAs in the presence of FBS. Given that Applicants have changed the serum dependence requirements from serum-independent to serum-dependent for two antibodies listed in Table 2 after filing of the instant application (see amendment to specification 10/18/2006 and the second declaration by Philip Thorpe under 37 CFR 1.132, dated 7/16/2007), given that Rote et al produced antibody 3SB in the presence of serum proteins, given the teachings of Luster et al, and Ran et al (above) that antibodies actually bind to serum proteins rather than the aminophospholipids themselves, and given the lack of data in the art and specification for serum-independent binding of antibodies to aminophospholipids that would also function as claimed and contemplated, one of ordinary skill in the art could reasonably believe that

antibodies 3SB and 9D2 are actually serum-dependent and do not bind directly to aminophospholipids as contemplated by the specification.

Therefore, in view of the state of the art, the quantity of experimentation necessary for making and using an antibody that will function as claimed and contemplated, the lack of guidance in the specification, and the absence of working examples for antibodies that actually bind PS and other aminophospholipids and would function as claimed and contemplated, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 1-11, 23, 94, 96-97, 102, and 115 are rejected under 35 U.S.C. 102(b) as being anticipated by Maneta-Peyret et al (J of Immunological Methods, 1988, 108:123-127) as evidenced by Bevers et al (Clinical Immunology, 2004, 112:150-160).

The claims are drawn to composition comprising a purified antibody, or antigen-binding fragment thereof, wherein said antibody binds to phosphatidylserine (PS) and

has substantially the same phospholipid binding profile as the monoclonal antibody 3G4, as determined by relative strength of reactivity in an ELISA, is PS=PA=PI=PG=CL>>PE, wherein > indicates at least 2-fold difference in phospholipid binding and >> indicates at least 10-fold difference in phospholipid binding, each at identical antibody concentrations; or an affinity for PS of at least equal to the affinity of 3G4 for PS; wherein the affinity of 3G4 for PS, as determined in said ELISA, has an EC_{50} value of 0.040 ug/ml; and wherein said ELISA comprises (i)-(iv) of claim 1 (claims 1, 9, 10, 11), wherein said antibody further binds to PA, PI, PG, CL or PE and effectively competes with 3G4 for binding to these phospholipids (claims 2-8), the composition of claim 1, wherein said antibody is prepared by a process comprising immunizing an animal with activated endothelial cells and selecting from the immunized animal an antibody as defined in claim 1 (claim 23); a composition comprising a purified antibody that binds to PS and has substantially the same phospholipid binding profile as 3G4 as defined in claim 94 and an affinity for PS as defined in claim 94 (claim 94); a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a biologically effective amount of a purified antibody or antigen-binding fragment thereof, wherein said antibody is an antibody as defined in claim 1 (claim 96); a purified antibody, or antigen-binding fragment thereof, wherein said antibody binds to PS, and has substantially the same phospholipid binding profile as 3G4 and affinity for PS as defined in claim 97 (claim 97, 115).

Maneta-Peyret et al teach a polyclonal antibodies that bind to phosphatidylserine (see pages 124-127; Figure 3; abstract).

As evidenced by Bevers et al, it is now known that these antibodies actually bind to serum proteins, of which the serum proteins then bind to aminophospholipids PS, PA, PI, PG, CL, and PE.

It would be expected that a subset of the polyclonal antibodies taught by Maneta-Peyret et al would have substantially the same phospholipid binding profile as the monoclonal antibody 3G4, as determined by relative strength of reactivity in an ELISA, is PS=PA=PI=PG=CL>>PE, wherein > indicates at least 2-fold difference in phospholipid binding and >> indicates at least 10-fold difference in phospholipid binding, each at identical antibody concentrations; or an affinity for PS of at least equal to the affinity of 3G4 for PS; wherein the affinity of 3G4 for PS, as determined in said ELISA, has an EC_{50} value of 0.040 ug/ml; and wherein said ELISA comprises adding PS to a solid support, blocking with a blocking buffer comprising 10% serum or bovine serum, adding a primary antibody diluted in said blocking buffer, wherein said primary antibody is said antibody that binds PS, and detecting bound primary antibody using a secondary antibody that binds to said primary antibody. The antibody of the prior art appears to be the same antibody as claimed, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable

differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Although the reference does not specifically state that the antibody can be produced by immunizing an animal with activated endothelial cells, the production of a product by a particular process does not impart novelty or unobviousness to a product when the same product is taught by the prior art. Therefore, even if a particular process used to prepare a product is novel and unobvious over the prior art, the product per se, even when limited to the particular process, is unpatentable over the same product taught by the prior art. See In re Kind, 207 F.2d 618, 620, 43 USPQ 400, 402 (CCPA 1939); In re Merz, 97 F.2d 599, 601, 38 USPQ 143, 144-145 (CCPA 1938); In re Bergy, 563 F.2d 1031, 1035, 195 USPQ 344, 348 (CCPA 1977) *vacated* 438 U.S. 902 (1978); and United States v. Ciba-Geigy Corp., 508 F. Supp. 1157, 1171, 211 USPQ 529, 543 (DNJ 1979).

4. Claims 1-19, 23, 51, 52, 94, 96-98, 102, 107, 115, and 120 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 00/02584, Thorpe and Ran, published 1/20/2000, IDS, as evidenced by Bevers et al (Clinical Immunology, 2004, 112:150-160).

The claims are drawn to a composition comprising a purified antibody, or antigen-binding fragment thereof, wherein said antibody binds to phosphatidylserine (PS) and has substantially the same phospholipid binding profile as the monoclonal antibody 3G4, as determined by relative strength of reactivity in an ELISA, is

PS=PA=PI=PG=CL>>PE, wherein > indicates at least 2-fold difference in phospholipid binding and >> indicates at least 10-fold difference in phospholipid binding, each at identical antibody concentrations; or an affinity for PS of at least equal to the affinity of 3G4 for PS; wherein the affinity of 3G4 for PS, as determined in said ELISA, has an EC_{50} value of 0.040 ug/ml; and wherein said ELISA comprises (i)-(iv) of claim 1 (claims 1, 9, 10, 11), wherein said antibody further binds to PA, PI, PG, CL or PE and effectively competes with 3G4 for binding to these phospholipids (claims 2-8), wherein said antibody is an monoclonal antibody (claim 12), wherein said antibody is an IgG antibody (claim 13), wherein said antibody is an antigen-binding fragment of an antibody, scFv, Fv, Fab', Fab, is camelized, single domain, humanized, chimeric recombinant or engineered (claims 14-17, 19), wherein said antibody comprises an antigen binding region of said antibody operatively attached to a human antibody framework or constant region (claim 18), the composition of claim 1 wherein said composition is a pharmaceutically acceptable composition and is formulated for parenteral administration (claims 51 and 52), a composition comprising a purified antibody that binds to PS and has substantially the same phospholipid binding profile as 3G4 as defined in claim 94 and an affinity for PS as defined in claim 94 (claim 94); a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a biologically effective amount of a purified antibody or antigen-binding fragment thereof, wherein said antibody is an antibody as defined in claim 1 (claim 96); a purified antibody, or antigen-binding fragment thereof, wherein said antibody binds to PS, and has substantially the same phospholipid binding profile as 3G4 and affinity for PS as defined in claim 97 (claim 97,

115); a hybridoma that produces a monoclonal antibody that binds to PS and has substantially the same phospholipid binding profile as 3G4 and affinity for PS as defined in claim 98 (claim 98, 120), a composition comprising a purified antibody, wherein a human antibody framework or constant region is operatively attached to an antigen-binding region of an antibody that binds to PS and effectively competes with 3G4 for binding to PS in an ELISA as recited in claim 107 (claim 107).

WO 00/02584 teaches the production of polyclonal and monoclonal anti-aminophospholipid antibodies(section E, p. 66-73) which can bind PS and PE (p. 20, lines 18-26). Antibodies include IgG antibodies (p. 23, lines 15-28; p. 71, line 29 through p. 73, line 9; p. 68, entire section E2). WO 00/02584 teaches that anti-phospholipid antibodies recognize phospholipids with protein cofactors (p. 82, lines 9-20; p. 83, lines 23-31). WO 00/02584 teaches that the antibody can be an antibody fragment, scFv, Fv, Fab', Fab, chimeric, recombinant, or bispecific, or humanized antibodies that have antigen binding regions attached to human antibody framework or constant region (p. 102-104, section E10; p. 93-96, section E7; p. 100-102, section E9; p. 151, lines 2-10; p. 152, lines 1-5; p. 27, lines 7-15). WO 00/02584 teaches pharmaceutical compositions comprising the antibodies and the treatment of cancer using said antibodies for targeting tumor vasculature (p. 104, section F; p. 48-61, section C; p. 110-118, section H). WO 00/02584 teaches parenteral formulation (p. 104-107, section F1). WO 00/02584 teaches that anti-phospholipid antibodies recognize phospholipids with protein cofactors (p. 82, lines 9-20; p. 83, lines 23-31). WO 00/02584 teaches hybridomas for producing monoclonal antibodies (p. 25-27).

As evidenced by Bevers et al, it is now known that these antibodies actually bind to serum proteins, of which the serum proteins then bind to aminophospholipids PS, PA, PI, PG, CL, and PE.

It would be expected that a subset of the polyclonal or monoclonal antibodies or antibodies produced by hybridomas taught by WO 00/02584 would have substantially the same phospholipid binding profile as the monoclonal antibody 3G4, as determined by relative strength of reactivity in an ELISA, is PS=PA=PI=PG=CL>>PE, wherein > indicates at least 2-fold difference in phospholipid binding and >> indicates at least 10-fold difference in phospholipid binding, each at identical antibody concentrations; or have an affinity for PS of at least equal to the affinity of 3G4 for PS; wherein the affinity of 3G4 for PS, as determined in said ELISA, has an EC_{50} value of 0.040 ug/ml; and wherein said ELISA comprises adding PS to a solid support, blocking with a blocking buffer comprising 10% serum or bovine serum, adding a primary antibody diluted in said blocking buffer, wherein said primary antibody is said antibody that binds PS, and detecting bound primary antibody using a secondary antibody that binds to said primary antibody; or effectively compete with 3G4 for binding to PS in the ELISA recited in claim 107. The antibody of the prior art appears to be the same antibody as claimed, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art

and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Although the reference does not specifically state that the antibody can be produced by immunizing an animal with activated endothelial cells, the production of a product by a particular process does not impart novelty or unobviousness to a product when the same product is taught by the prior art. Therefore, even if a particular process used to prepare a product is novel and unobvious over the prior art, the product per se, even when limited to the particular process, is unpatentable over the same product taught by the prior art. See In re Kind, 207 F.2d 618, 620, 43 USPQ 400, 402 (CCPA 1939); In re Merz, 97 F.2d 599, 601, 38 USPQ 143, 144-145 (CCPA 1938); In re Bergy, 563 F.2d 1031, 1035, 195 USPQ 344, 348 (CCPA 1977) *vacated* 438 U.S. 902 (1978); and United States v. Ciba-Geigy Corp., 508 F. Supp. 1157, 1171, 211 USPQ 529, 543 (DNJ 1979).

Relevant Arguments

5. Applicants argue that many specific monoclonal antibodies made by Rote and Umeda, as taught in WO 00/02584, are distinguished from antibody 3G4 because they do not share the same binding profile as 3G4. Applicants submitted a third Thorpe declaration, 7/16/07, that demonstrates that antibody 3SB, produced by Rote et al and also taught by WO 00/02584, does not effectively compete with antibody 3G4 for binding to PS (p. 27-31).

Applicants further argue that although anti-PS antibodies could be made at the time of WO 00/02584, the available techniques suffered from different drawbacks and limitations. The prior art methods were all different to and lacked the advantages of the immunization techniques of the present invention, and would not be expected to produce antibodies with the desirable characteristics of 3G4.

Applicants argue that they clearly distinguished all claims from prior art by incorporating the language of specific binding profiles and affinities previously found to be novel and non-obvious (p. 32).

The arguments have been carefully considered but are not found persuasive. The rejection of claims 1-19, 23, 51, 52, 94, 96-98, 102, 107, 115, and 120 under USC 102(b) above now addresses that the art teaches production of both polyclonal and monoclonal antibodies against aminophospholipids, wherein it would be expected that a subset of the polyclonal or monoclonal antibodies taught by WO 00/02584 would have substantially the same phospholipid binding profile as the monoclonal antibody 3G4, or an affinity for PS of at least equal to the affinity of 3G4 for PS as recited in claim 1. While Applicants have shown that the binding affinity profiles for different phospholipids vary among monoclonal antibodies produced by Umeda and Rote (taught by WO 00/02584), and that the binding profiles for some of these monoclonal antibodies differ from the binding profile of antibody 3G4, Applicants have not demonstrated that it would not be expected that any monoclonal or polyclonal antibodies taught by the prior art could have the claimed binding profiles or binding affinity as referenced to 3G4 in claim 1. Applicants rely on the methods of making antibodies as the argument for the

difference between the claimed antibodies and the prior art antibodies, however, it is clear from the art and the specification that one of skill in the art could reasonably expect that the polyclonal and monoclonal antibodies taught by the prior art would encompass a subset of antibodies that would have the claimed affinities and binding profiles. In other words, the method of making antibodies used by Umeda produced antibodies with very different binding profiles, the method of making antibodies used by Rote et al also produced antibodies with very different binding profiles, the method of making antibodies used by the instant application also produced antibodies with very different binding profiles and different binding affinities to PS (Table 2, p. 243; Table 3, p. 245; Table 4, p. 246), hence one of skill in the art could *not* reasonably conclude that the methods of making antibodies impart novelty on the binding profiles or affinities of all antibodies produced using any one specific method, or that any specific method of making antibodies taught in the prior art would *not* produce an antibody with the claimed binding profiles and affinities. Applicants have not shown how the antibodies or hybridomas of the prior art are different from the claimed antibodies.

6. Claims 1-12, 23, 51, 52, 94, 96-98, 102, 115, and 120 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 6,300,308, Schroit, filed 12/30/1998, issued 10/9/2001, as evidenced by Bevers et al (Clinical Immunology, 2004, 112:150-160).

The claims are drawn to a composition comprising a purified antibody, or antigen-binding fragment thereof, wherein said antibody binds to phosphatidylserine (PS) and has substantially the same phospholipid binding profile as the monoclonal antibody 3G4, as determined by relative strength of reactivity in an ELISA, is PS=PA=PI=PG=CL>>PE, wherein > indicates at least 2-fold difference in phospholipid binding and >> indicates at least 10-fold difference in phospholipid binding, each at identical antibody concentrations; or an affinity for PS of at least equal to the affinity of 3G4 for PS; wherein the affinity of 3G4 for PS, as determined in said ELISA, has an EC_{50} value of 0.040 ug/ml; and wherein said ELISA comprises (i)-(iv) of claim 1 (claims 1, 9, 10, 11), wherein said antibody further binds to PA, PI, PG, CL or PE and effectively competes with 3G4 for binding to these phospholipids (claims 2-8), wherein said antibody is monoclonal (claim 12), the composition of claim 1, wherein said composition is a pharmaceutically acceptable composition and is formulated for parenteral administration (claims 51, 52), the composition of claim 1, wherein said antibody is prepared by a process comprising immunizing an animal with activated endothelial cells and selecting from the immunized animal an antibody as defined in claim 1 (claim 23); a composition comprising a purified antibody that binds to PS and has substantially the same phospholipid binding profile as 3G4 as defined in claim 94 and an affinity for PS as defined in claim 94 (claim 94); a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a biologically effective amount of a purified antibody or antigen-binding fragment thereof, wherein said antibody is an antibody as defined in claim 1 (claim 96); a purified antibody, or antigen-binding fragment thereof,

wherein said antibody binds to PS, and has substantially the same phospholipid binding profile as 3G4 and affinity for PS as defined in claim 97 (claim 97, 115); a hybridoma that produces a monoclonal antibody that binds to PS and has substantially the same phospholipid binding profile as 3G4 and affinity for PS as defined in claim 98 (claim 98, 120).

Schroit teach the production of polyclonal and monoclonal antibodies that bind to phosphatidylserine (col. 2, lines 1-52; col. 3, lines 12-36; col. 4, lines 38-48; col. 5, lines 4-8; col. 8, lines 40 through col. 9, line 56; col. 13, line 55 through col. 14, line 41; Example 1). Schroit demonstrate the affinity of polyclonal antibodies to PS, PE, PA, and PG in Figure 3 (col. 23, line 54-67). Schroit teach these antibodies can be comprised in pharmaceutically acceptable compositions and for parenteral administration (col. 7, lines 4-11; col. 16, line 45 through col. 18). Schroit teach hybridomas producing monoclonal antibodies (col. 9, line 57 through col. 10, line 52).

As evidenced by Bevers et al, it is now known that these antibodies actually bind to serum proteins, of which the serum proteins then bind to aminophospholipids PS, PA, PI, PG, CL, and PE.

It would be expected that a subset of the polyclonal or monoclonal antibodies or antibodies produced by hybridomas taught by Schroit would have substantially the same phospholipid binding profile as the monoclonal antibody 3G4, as determined by relative strength of reactivity in an ELISA, is PS=PA=PI=PG=CL>>PE, wherein > indicates at least 2-fold difference in phospholipid binding and >> indicates at least 10-fold difference in phospholipid binding, each at identical antibody concentrations; or an

affinity for PS of at least equal to the affinity of 3G4 for PS; wherein the affinity of 3G4 for PS, as determined in said ELISA, has an EC_{50} value of 0.040 ug/ml; and wherein said ELISA comprises adding PS to a solid support, blocking with a blocking buffer comprising 10% serum or bovine serum, adding a primary antibody diluted in said blocking buffer, wherein said primary antibody is said antibody that binds PS, and detecting bound primary antibody using a secondary antibody that binds to said primary antibody. The antibody of the prior art appears to be the same antibody as claimed, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Although the reference does not specifically state that the antibody can be produced by immunizing an animal with activated endothelial cells, the production of a product by a particular process does not impart novelty or unobviousness to a product when the same product is taught by the prior art. Therefore, even if a particular process used to prepare a product is novel and unobvious over the prior art, the product per se, even when limited to the particular process, is unpatentable over the same product taught by the prior art. See In re Kind, 207 F.2d 618, 620, 43 USPQ 400, 402 (CCPA

1939); In re Merz, 97 F.2d 599, 601, 38 USPQ 143, 144-145 (CCPA 1938); In re Bergy, 563 F.2d 1031, 1035, 195 USPQ 344, 348 (CCPA 1977) *vacated* 438 U.S. 902 (1978); and United States v. Ciba-Geigy Corp., 508 F. Supp. 1157, 1171, 211 USPQ 529, 543 (DNJ 1979).

7. All other rejections recited in the Office Action mailed January 12, 2007 are hereby withdrawn.

8. **Conclusion:** Claims 106, 112, 117, and 122 are allowed. Claims 1-19, 23, 51, 52, 94, 96-99, 102, 105, 107, 111, 115, 116, 120, and 121 are rejected.

Applicants filed a terminal disclaimer 7/16/2007 to overcome the provisional double patenting rejection with Application Nos. 10/642,071, 10/642,120, 10/642,058, 10/642,116, 10/642,119, 10/642,065, and 10/620,850.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Laura B Goddard, Ph.D.
Examiner
Art Unit 1642